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EXAMINER	
RAE, CHARLESWORTH E	
ART UNIT	**PAPER NUMBER**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/784,145	MIYACHI ET AL.	
	Examiner	Art Unit	
	Charleswort Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/06; 10/25/05; 12/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-34 are currently pending in this application and are the subject of the Office action.

Claim of benefit of priority

Applicant's statement that the specification has been amended to reflect applicant's claim to benefit of priority from U.S. Provisional Patent Application No. 60/448,970, filed February 21, 2003, is acknowledged and made of record.

Applicant's claim to benefit is granted and entered of record.

Nonstatutory Obviousness-Type Double-Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422

F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-34 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-38 of copending U.S. Patent Application No. 10/752,523, in view of Elan Pharma, FDA Approved Labeling Text, 03/27/200, U.S. Food and Drug Administration, http:/www,fda.gov/cedr/foi/label/2000/20789lbl.pdf, pages 1-24. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

In particular, claim 1 of copending application '523 is directed to a method of using zonisamide as an adjunctive therapy for partial seizures to improve the safety of such therapy comprising the step of providing a patient with a therapeutically effective amount of zonisamide and informing the patient of the patient's guardian during the course of zonisamide therapy that muscle stiffness, muscle pain, ... fever, discolored

urine ... require prompt medical evaluation if such symptoms are experienced by the patient.

Elan teaches the following: zonisamide as **adjunctive therapy** in the treatment of **partial seizures** in adults with epilepsy (page 6); **information for patients** (page 10 to page 11) and **Patient Information Leaflet** (pages 22-24), which is reasonably construed to meet the limitation of the instant claim 1 method step of *"informing the patient ... during the course of zonisamide therapy that ... renal insufficiency, fatigue, anemia ...that require prompt medical evaluation if such symptoms are experienced by the patient"* ; **100 mg capsules**, which are reasonably construed to meet the *"unit dose form"* limitation recited in instant claim 3, for example (page 21); capsules are supplied in **bottles of 100**, which are reasonably construed to meet the *"multiple doses"* limitation recited in instant claim 4, for example; zonisamide doses of 1**00-600 mg/day are effective** (page 20), which overlaps with the dosage range recited in instant claim 2, for example; patients should contact their physician immediately if they develop signs or symptoms such as sudden back pain, abdominal pain, and/or **blood in the urine** (that could indicate a kidney stone) (page 11); patients with **renal or hepatic disease should be treated with caution, and might require slower titration and more frequent monitoring** (page 10, first paragraph; and page 20, last paragraph to page 21, line 2). Elan teaches that **concomitant administration of phenytoin and carbamazepine** increases zonisamide plasma clearance (page 3, 4th paragraph); someone of skill in the art could reasonably construe this limitation to mean the concomitant administration of a therapeutically effective amount of phenytoin or

carbamazepine with zonisamide adjunctive therapy. Instant claim 29 recites the term *"therapeutically effective amount of at least one other anti-epileptic drug."* Elan teach a number of zonisamide side effects/adverse effects, which include **fatigue** (pages 14, and 17), mental slowing (page 17), mental slowing (page16), confusion (page 16), dry mouth/thirst (page 16, and page 18), nystagmus (page 16), paresthesia (page 16), dehydration (page 18), hypertension (page 18), hypotension (page 18), tachycardia (page 18), **anemia** (page 18), **SGOT increased** (page 18), SGPT increased (page 18), lactic dehydrogenase (LDH) increased (page 18), and **hematuria** (page 19).

To the extent that the patient population (i.e. partial seizure patients) and the dose of zonisamide (i.e. 25 mg to 600 mg) of the instant invention overlaps with the reference, the side effects/untoward effects of zonisamide recited in instant claim 1, for example, are coextensive with its administration. Thus, the instant method is deemed to be an obvious variant of the reference claims.

Thus, claims 1-34 are deemed obvious variants of the limitations of the subject matter claimed in copending application '523.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending applications have not in fact been patented.

Claims 1-34 are also rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-41 of copending U.S. Patent Application No. 10/752,522. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims.

In particular, claim 1 of copending application '522 is directed to a method of using zonisamide as an adjunctive therapy for partial seizures to improve the safety of such therapy comprising the step of providing a patient with a therapeutically effective amount of zonisamide and informing the patient of the patient's guardian during the course of zonisamide therapy that dehydration, hyperthermia, muscular rigidity, altered mental status ... require prompt medical evaluation if such symptoms are experienced by the patient. To the extent that the patient population (i.e. partial seizure patients) and the dose of zonisamide (i.e. 25 mg to 600 mg) overlap, the side effects/untoward effects of the drug are coextensive with its administration. Thus, the instant method is deemed to be an obvious variant of the reference claims.

Thus, claims 1-34 are deemed obvious variants of the limitations of the subject matter claimed in copending application '522.

This is a provisional obviousness-type double patenting rejection because the conflicting claims of the copending applications have not in fact been patented.

For the same reasons as stated above, claims 1-34 are also provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 of copending U.S. Patent Application No. 10/644,935; claims 1-36 of copending U.S. Patent Application No. 10/752,516; claims 1-39 of copending U.S. Patent Application No. 10/753,957; and claims 1-36 of copending U.S. Patent Application No. 10/752,515. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are either anticipated by, or would have been obvious in view of the referenced claims. These are

provisional obviousness-type double patenting rejections because the conflicting claims of the copending applications have not in fact been patented.

In reviewing the continuity data, it is noted that applicant has numerous issued patent and pending applications encompassing the same or similar subject matter of the instant application. Applicant should review all subject matter considered the same or similar, and submit the appropriate Terminal Disclaimer(s). For example, application No. 10/753,955, and 10/753,956.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1- 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 6, and 11 recite the term *" such therapy."* This term is vague and indefinite because it is unclear what the term specifically relates to. The term could reasonably be interpreted to relate to back to "adjunctive therapy," or, non-adjunctive therapy, in view of the dictionary definition of the term "adjunct." This rejection may be overcome by deleting the term "such therapy" and replacing it with the term "said adjunctive therapy" provided this does not add new matter to the specification as originally filed.

Dependent claims 2-5, 7-10, and 12-14 are rejected for the same reasons as these claims fail to correct the deficiency of the independent claim 1 from which they depend.

Claims 1, 6, and 11 recite the step of *"providing a patient with a therapeutically effective amount of zonisamide"* and the step of *"informing the patient or the patient's guardian during the course of zonisamide therapy."* However, these steps are not specifically related to "prompt medical evaluation," which is considered essential for the practicing of the instant method. These claims are rejected under 112, second paragraph, for being indefinite for omitting matter disclosed to be essential to the invention as described in the specification.

Dependent claims 2-5, 7-10, and 12-14 are rejected for the same reasons as these claims fail to correct the deficiency of the independent claim 1 from which they depend.

Claim 1 recites the terms *"increased frequency or duration of infection"* and *"odor are symptoms."* These terms are indefinite because it is not clear what the terms mean due to apparent typographical errors.

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of using zonisamide as an adjunctive therapy for partial seizures to improve the safety of zonisamide i.e. zonisamide-induced adverse effects, including MGUS, does not reasonably provide enablement to improve

the safety profile of other concomitant drugs, for example, phenytoin, phenobarbital, or primidone. This is a scope enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a method for improving the safety profile of zonisamide. Applicant asserts that the instant invention is directed to methods of using zonisamide for a regulatory agency approved use (e.g., as an adjunctive therapy for partial seizures) and that the methods improve the safety of zonisamide therapy for patients receiving administrations of the drug, or those who are in need of zonisamide therapy (U.S. Patent Application Publication No. 20050059718, paragraph 0008).

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the pharmaceutical art is generally unpredictable, requiring each embodiment to be individually assessed for physiological activity. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)). For example, the development of a serious disorder following the development of hyperproteinemia, for example, may occur range from 2 to 29 years of exposure to zonisamide. Thus, one skilled in the art

would not be able to extrapolate the disclosed teachings of the claimed invention to all conditions of hypercalcemia, renal insufficiency, fatigue, anemia, bone pain, spontaneous fractures, increased frequency or duration of infection, or abnormal urine color or odor are symptoms of MGUS, SMM, or MM that require prompt medical evaluation if such symptoms are experienced by the patient.

Elan teaches that zonisamide has not been found to be safe and effective in treating patients below the age of 16 (Elan Pharma (Zonisamide Approvable Labeling, Published 03/27/2000; see page 14, first paragraph).

Asai et al. disclose a single case of a 39-year old man who developed hyperproteinemia (8.6 g/dl) while on zonisamide alone for treatment of generalized seizure; the index patient received zonisamide 200 mg daily for 5 years, followed by 100 mg daily for 10 years ((Asai et al. Smoldering myeloma associated with zonisamide treatment. Internal Medicine. 2002;41(2):138-141; see page 138, column 2) . Laboratory examination showed an elevated serum level of immunoglobulin G (IgG, 3,680 mg/dl) with suppressed levels of IgM (38 mg/dl) and IgA (40 mg/dl); Bence-Jones protein in urine was not demonstrated Serum levels of creatinine, calcium and B2-microglobulin were not elevated. A review of the index patient's medical record revealed gradual increases of serum total protein from 6.5 g/dl (normal range: 6.5-8 g/dl) in 1993 to 8.2 g/dl in 1998 during treatment with zonisamide (page 138, column 2). Asai et al. disclose that the clinical features of malignant B-lymphocyte or plasma cell disorder were absent, including osteolysis, suppression of hemopoiesis, hypercalcemia and renal dysfunction the patient was diagnosed as having smoldering myeloma (page 140,

column 1, first full paragraph). Asai et al. report that use of some anticonvulsants such as phenytoin, phenobarbital and primidone have been associated with multiple myeloma (page 140, column 1, second full paragraph). Asai et al. report that zonisamide was discontinued in the patient and replaced with sodium valproate for treatment of seizure; no increase in the serum level of total protein nor IgG was observed during the 13 month observation period. Asai et al. disclose that a few patients with IgA and/or IgG deficiency have been reported in association with zonisamide (page 140, column 2, first full paragraph, lines 1-4). Asai et al. recommend a periodical examination of serum levels and patterns of gammaglobulin when patients are receiving zonisamide as well as other convulsants.

Kyle teaches that serum proteins should be analyzed by electrophoresis when multiple myeloma (MM), macroglobulinemia, or amyloidosis is suspected; electrophoresis is also indicated in any patient with unexplained weakness or fatigue, anemia, increased erythrocyte sedimentation rate, back pain, osteoporosis or osteolytic lesions or fracture, immunoglobulin deficiency, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections (page 2154, column 2, third full paragraph). Kyle. The monoclonal gammopathies. Clin. Chem. 1994; 40/11(B): 2154-2161). Kyle teaches that the term monoclonal gammopathy of undertermined significance (MGUS) denotes the presence of an M-protein in persons without evidence of myeloma, macroglobulinemia, amyloidosis, or other related diseases (page 2158, column 1, first full paragraph). Kyle teaches that the interval between the recognition of the M-protein and the diagnosis of a serious disease ranged from 2 to 29 years, but no features at

diagnosis were useful for distinguishing patients who did not progress from those in whom a malignant change developed (page 2158, column 1, last line to column 2, line 11).

Fujimoto et al. teach that no significant correlation was found between the dose or serum concentration of zonisamide and immunoglobulin levels in 19 patients who received zonisamide (AD-810) for a maximum of 48 months in daily dosage of 200-700 mg for refractory epilepsy who had been receiving multiple antiepileptic drugs (Fujimoto et al. Effect of zonisamide on serum immunoglobulins. Arzmeim-Forsch/Drug Res. 1990; 40(11), nr 8, pages 855-858, abstract only - already made of record by applicant).

2. The breadth of the claims

The claims relatively very broad. For example, claim 1 recites the term "improve the safety of such therapy," which reasonably encompass other therapies besides "zonisamide adjunctive therapy" (Compact Oxford English Dictionary; see term "adjunct"). The prompt medical evaluation that would be required in practicing the instant method would necessarily vary depending upon the specific cause of the hypercalcemia, or fatigue, or anemia, or bone pain etc, presence of coexisting diseases or concomitant drugs, or the duration of the exposure to zonisamide. Also, claim 1 recites the term *"informing the patient or the patient's guardian during the course of zonisamide therapy,"* which could reasonably be construed to mean 1 day, or 1 month, or 1 year, or 60 years after the initiation of zonisamide therapy, which would seriously diminish the level of predictably in practicing the claimed invention; the specific means by which the "informing of the patient or the patient's guardian" is also not disclosed.

Claim 2 recites the term "wherein the therapeutically effective amount of zonisamide is from 25 to 600 mg," however, the therapeutically effective dosage range appears to be at least 100 mg. No data is disclosed to correlate a daily dose of zonisamide 25 mg with the development of MGUS, or SMM, or MM, for example. Further, claim 1 recites the term "prompt medical evaluation," which could reasonably be construed to mean 2 years or 29 years, if one considers the wide time interval for developing, hyperproteinemia, for example. However, abrupt withdrawl of zonisamide in patients with epilepsy may precipitate increased seizure frequency or status epilepticus; dose reduction or discontinuation of zobnisamide should therefore be done gradually (Elan page 7, 4th full paragraph). In addition, instant claims reasonably encompass partial seizures patients of any age, including children under 16 years even though the safety and efficacy of zonisamide has not been established in children under 16 years of age.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification discloses only a few anedoctal reports of MGUS and SMM; no case of zonisamide-induced MM is disclosed. The case of zonisamide-induced SMM occurred in a patient who received znoisamide as the single therapy, rather than as adjunctive therapy; the dose of zonisamide was between 100 to 200 mg daily for 10 years. In fact, the specification provides only limited direction or guidance for determining the specific time for informing the patient, or the specific time to seek prompt medical evaluation. Thus, the applicant at best has provided specific direction or guidance only for a general protocol for improving the safety zonisamide-induced

hyperproteinemia. No reasonably specific guidance is provided concerning useful therapeutic protocols to improve the safety of zonisamide-induced MM in partial seizure patients using zonisamide as adjunctive therapy, however.

4. The quantity of experimentation necessary

In view of the teaching of the prior art and the limited disclosure of the instant specification, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention partial seizure patients who receive zonisamide 25 mg daily as adjunctive therapy. Thus, based on the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as methods for improving the safety of zonisamide adjuctive therapy and other concomitant therapies.

For the reasons stated above, claims 1-34 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

112 – First Paragraph – Written Description

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, because while the specification provides written description for a method of using zonisamide as an adjunctive therapy for partial seizures to improve the safety of zonisamide i.e. zonisamide-induced adverse effects, including MGUS, it does not reasonably provide

written description for a method to improve the safety profile of other concomitant drugs, for example, phenytoin, phenobarbital, or primidone, which are also associated with causing identical/similar adverse effects, such as e.g. phenytoin-induced multiple myeloma. Thus, claims 1-34 are rejected for lack of written description.

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15 are rejected under 35 USC 102(b) as being anticipated by Elan Pharma (Zonisamide Approvable Labeling, Published 03/27/2000).

For the purposes of this rejection the term "such therapy" as discussed in the above rejection under 112, second paragraph, is construed to mean zonisamide adjunctive therapy.

Elan teaches the following: zonisamide as **adjunctive therapy** in the treatment of **partial seizures** in adults with epilepsy (page 6); **information for patients** (page 10 to page 11) and **Patient Information Leaflet** (pages 22-24), which is reasonably construed to meet the limitation of the instant claim 1 method step of *"informing the patient ... during the course of zonisamide therapy that ... renal insufficiency, fatigue,*

anemia ...that require prompt medical evaluation if such symptoms are experienced by the patient" ; **100 mg capsules**, which are reasonably construed to meet the *"unit dose form"* limitation recited in instant claim 3, for example (page 21); capsules are supplied in **bottles of 100**, which are reasonably construed to meet the *"multiple doses"* limitation recited in instant claim 4, for example; zonisamide doses of **100-600 mg/day are effective** (page 20), which overlaps with the dosage range recited in instant claim 2, for example; patients should contact their physician immediately if they develop signs or symptoms such as sudden back pain, abdominal pain, and/or **blood in the urine** (that could indicate a kidney stone) (page 11); patients with **renal or hepatic disease should be treated with caution, and might require slower titration and more frequent monitoring** (page 10, first paragraph; and page 20, last paragraph to page 21, line 2). Elan teaches that **concomitant administration of phenytoin and carbamazepine** increases zonisamide plasma clearance (page 3, 4th paragraph); someone of skill in the art could reasonably construe this limitation to mean the concomitant administration of a therapeutically effective amount of phenytoin or carbamazepine with zonisamide adjunctive therapy. Elan teaches a number of zonisamide side effects/adverse effects, which include **fatigue** (pages 14, and 17), mental slowing (page 17), mental slowing (page16), confusion (page 16), dry mouth/thirst (page 16, and page 18), nystagmus (page 16), paresthesia (page 16), dehydration (page 18), hypertension (page 18), hypotension (page 18), tachycardia (page 18), **anemia** (page 18), **SGOT increased** (page 18), SGPT increased (page 18), lactic dehydrogenase (LDH) increased (page 18), and **hematuria** (page 19).

Claim 6 recites the term *"improve the health."* This term given its broadest reasonable possible interpretation is construed to mean the administration of an effective amount of zonisamide as taught by Elan.

Claim 11 recites the term *"reduce the risk"* of MGUS, SMM, or MM. This term given its broadest reasonable possible interpretation is construed to encompass any patient with or without MGUS, SMM, or MM who is treated with zonisamide, which is reasonably satisfed by the teaching of Elan of administering zonisamide to adults with partial seizures.

Thus, claims 1-15 are rejected as being anticipated by Elan.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> **(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 16-34 are rejected as being unpatentable over Elan Pharma (Zonisamide Approvable Labeling, Published 03/27/2000), in view of Asai Asai et al. Smoldering myeloma associated with zonisamide treatment. Internal Medicine. 2002;41(2):138-141), in view of Kyle (Kyle. The monoclonal gammopathies. Clin. Chem. 1994; 40/11(B): 2154-2161).

For the purposes of this rejection the term "such therapy" as discussed in the above rejection under 112, second paragraph, is construed to mean zonisamide adjunctive therapy.

Claim 16 recites the term *"enhancing the safety profile."* This term is reasonably construed to be an inherent feature of the **information for patients** (page 10 to page 11) and **Patient Information Leaflet** (pages 22-24), as taught by Elan.

Claim 17 recites the term *"improving patient outcome."* This term is reasonably construed to be an inherent feature of the **information for patients** (page 10 to page 11) and **Patient Information Leaflet** (pages 22-24), as taught by Elan.

The limitations with respect to "informing a prescribing physician ...," "advising the physician ...," "recommending that a laboratory test ...," as recited in claims 16, 17, and "providing packaging ... along with information providing a warning ...," as recited in claims 24, 30, and 32, and "monitoring a patient who is receiving administration of zonisamide ...," as recited in claim 33, are reasonably construed to within the scope and knowledge of a skilled artisan in the art. Judicial notice is taken that the packaging and labeling instructing use of a

composition is old and well known. The sole difference between the claimed and prior art articles is the printed matter information means indicating the known adverse effects of zonisamide. However, the printed matter e.g. patient information, does not possess a "functional relationship" with the administering of a therapeutically effective amount of zonisamide as adjunctive therapy in patients with partial seizures, and accordingly, is not granted any patentable weight. Thus, the claimed invention was obvious to one of ordinary skill in the art at the time of the instant invention was made.

The above discussion of Elan in connection with the 102(b) rejection is incorporated by reference. However, Elan does not specifically mention how to advise the physician or an emergency medical worker to monitor a patient who is prescribed zonisamide as said partial seizure for said one or more symptoms "recommending that a laboratory test for paraproteinemia, M-spike protein in the serum, Bence-Jones proteint in urine, or suppression of normal immunoglobulin levels be performed ... if the test reveals an abnormal result for that patient ... consider removing, reucing, or tapering off zonisamide dosing in the patient while initiating appropriate supportive therapy.

Asai et al. disclose a case of a 39-year old man who was suspected of developing hyperlipoproteinemia and smoldering myeloma while being treated with zonisamide; the patient's M-protein did not increase over the 13 months the patient was taken off zinosamide and placed on valproate (abstract) (Asai et al. Smoldering myeloma associated with zonisamide treatment. Internal Medicine. 2002;41(2):138-141). Asai et al. disclose a single case of a 39-year old man who developed hyperproteinemia (8.6 g/dl) while on zonisamide alone for treatment of generalized

seizure; the index patient received zonisamide 200 mg daily for 5 years, followed by 100 mg daily for 10 years (page 138, column 2) . Laboratory examination showed an elevated serum level of immunoglobulin G (IgG, 3,680 mg/dl) with suppressed levels of IgM (38 mg/dl) and IgA (40 mg/dl); Bence-Jones protein in urine was not demonstrated; and serum levels of creatinine, calcium and B2-microglobulin were not elevated. A review of the index patient's medical record revealed gradual increases of serum total protein from 6.5 g/dl (normal range: 6.5-8 g/dl) in 1993 to 8.2 g/dl in 1998 during treatment with zonisamide (page 138, column 2). Asai et al. disclose that the clinical features of malignant B-lymphocyte or plasma cell disorder were absent, including osteolysis, suppression of hemopoiesis, hypercalcemia and renal dysfunction the patient was diagnosed as having smoldering myeloma (page 140, column 1, first full paragraph). Asai et al. report that use of some anticonvulsants such as phenytoin, phenobarbital and primidone have been associated with multiple myeloma (page 140, column 1, second full paragraph). Asai et al. report that zinisamide was discontinued in the patient and replaced with sodium valproate for treatment of seizure; no increase in the serum level of total protein nor IgG was observed during the 13 month observation period. Asai et al. disclose that a few patients with IgA and/or IgG deficiency have been reported in association with zonisamide (page 140, column 2, first full paragraph, lines 1-4). Asai et al. recommend a periodical examination of serum levels and patterns of gammaglobulin when patients are receiving zonisamide as well as other convulsants.

Kyle teaches that serum proteins should be analyzed by electrophoresis when multiple myeloma (MM), macroglobulinemia, or amyloidosis is suspected;

electrophoresis is also indicated in any patient with unexplained weakness or fatigue, anemia, increased erythrocyte sedimentation rate, back pain, osteoporosis or osteolytic lesions or fracture, immunoglobulin deficiency, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections (page 2154, column 2, third full paragraph). Kyle. The monoclonal gammopathies. Clin. Chem. 1994; 40/11(B): 2154-2161). Kyle teaches that the term monoclonal gammopathy of undertermined significance (MGUS) denotes the presence of an M-protein in persons without evidence of myeloma, macroglobulinemia, amyloidosis, or other related diseases (page 2158, column 1, first full paragraph). Kyle teaches that the interval between the recognition of the M-protein and the diagnosis of a serious disease ranged from 2 to 29 years, but no features at diagnosis were useful for distinguishing patients who did not progress from those in whom a malignant change developed (page 2158, column 1, last line to column 2, line 11).

Based on the teaching of Kyle that serum proteins should be analyzed by electrophoresis when multiple myeloma (MM), macroglobulinemia, or amyloidosis is suspected; electrophoresis is also indicated in any patient with unexplained weakness or fatigue, anemia, increased erythrocyte sedimentation rate, back pain, osteoporosis or osteolytic lesions or fracture, immunoglobulin deficiency, hypercalcemia, Bence Jones proteinuria, renal insufficiency, or recurrent infections (page 2154, column 2, third full paragraph), someone of skill in the art at the time the instant invention was made would have been motivated to combine the teachings of Elan, and Asia et al and Kyle to arrive at the instant inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant invention with a reasonable expectation of success in view of Elan, and Asai et al., and Kyle.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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11 June 2007
CER

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PRIMARY EXAMINER